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MOTION SICKNESS DRUGS

Of drugs claimed to prevent or relieve motion sickness, all except scopolamine have antihistaminic properties, and all are more or less effective. Different "controlled and double-blind" trials of these drugs give contradictory results, and no one drug appears to be of outstanding effectiveness.

The contradiction is not surprising in view of the difficulty of determining the effectiveness of these drugs. Not only is there great variation in susceptibility to motion sickness, but psychological as well as labyrinthine stimuli affect the response to motion, and a placebo alone often confers protection (E. M. Glaser and R. A. McCance, Lancet, 1:853, 1959). Moreover, the conditions responsible for motion sickness vary not only with the means of transportation, but also from trip to trip in the same type of vehicle.

CONTROLLED TRIALS - Among the most important of the controlled trials were those conducted by an armed services motion sickness team during a series of transport sailings ("Report of Study by Army, Navy, Air Force Motion Sickness Team," JAMA, 160:755, 1956; R. Trumbull, et al., Clin. Pharm. & Ther., 1:280, 1960). These investigators got about equally good results with three different drugs: Meclizine, USP (Bonine - Pfizer), 50 mg. once daily; Cyclizine, USP (Marezine - Burroughs Wellcome), 50 mg. three times a day; and Promethazine, USP (Phenergan - Wyeth), 25 mg. three times a day. Phenergan caused considerably more drowsiness than the other drugs. Diphenhydramine, USP (Benadryl - Parke, Davis), 50 mg. three times a day and Dimenhydrinate, USP (Dramamine - Searle), 100 mg. three times a day, were almost as effective, but they may also cause drowsiness. Chlorpromazine, USP (Thorazine - SKF) was ineffective. Scopolamine was also ineffective — a finding in direct conflict with the observation of Glaser and McCance (cited above) that scopolamine was superior to Marezine, Bonine, Phenergan, and other drugs. Glaser and McCance tested the drugs during a two-hour exposure to simulated heavy seas. Barbiturate drugs, once used extensively for motion sickness, were considered to be of little importance by two leading investigators, H. I. Chinn and P. K. Smith (Pharm. Rev., 7:33, 1955).

CHOICE OF DRUGS - Despite the conflicting results, scopolamine may be worth trying in a single 1-mg. dose. Such side effects as dry mouth, blurred vision, excitement, and hallucinations bar its continued use during long exposure. It is contraindicated in patients with glaucoma. Alternatively, or for continuous

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protection over longer periods, the drugs found effective in the armed forces study might be tried. (Persons who are often troubled by motion sickness should be advised to stay near the middle of a ship or plane, or in the front seat of a car, where linear acceleration is minimal.) Where drowsiness can have serious consequences, as in driving a car or piloting a plane, no drug should be used without prior trial.

ANTIEMETICS AND POSTOPERATIVE NAUSEA AND VOMITING

Relatively few patients vomit postoperatively, and no antiemetic drug can be used without some risk. Medical Letter consultants therefore believe that antiemetics should not be employed prophylactically but should be used only when significant nausea and vomiting have occurred, especially when vomiting threatens the results of surgery (of the eye, for example).

This belief is contrary to the views expressed in many enthusiastic reports on the prophylactic use of antiemetics after surgery. But most of these reports fail to take into account the difficulty of determining frequency and severity of vomiting without constant monitoring, the even greater difficulty of evaluating such subjective phenomena as nausea, and the multiplicity of causes of postoperative vomiting (narcotics, gastric dilation, ileus, peritoneal irritation, fluid and electrolyte disturbances, emotional factors and others).

All antiemetics may have undesirable side effects such as hypotension (often difficult to treat when caused by phenothiazines) and prolongation of the time from the end of anesthesia to the beginning of responsiveness. The phenothiazines may also cause restlessness (akathisia), twitching, nuchal rigidity, or other dyskinetic symptoms, even with brief use. The side effects of the antiemetics are sometimes more serious than the nausea and vomiting they are intended to prevent.

RESULTS OF TRIALS - Though no one antiemetic is uniformly successful, many different agents are frequently helpful. In one well-controlled study of patients receiving nitrous oxide-ether (M. R. Knapp and H. K. Beecher, JAMA, 160: 376, 1956), 150 mg. of pentobarbital was about equal to 50 mg. of chlorpromazine (Thorazine - SKF) in antiemetic effect, and it appeared to be somewhat safer.

In another controlled study (J. W. Bellville, et al., JAMA, 172: 1488, 1960 and Clin. Pharm. and Ther., 1: 590, 1960), the incidence of nausea or vomiting was reduced to about 5 per cent (compared with about 15 per cent in the controls) by all of the following drugs, given intramuscularly on arrival of the patient in the recovery room: 2 mg. of fluphenazine (Prolixin - Squibb; Permitil - White); 12.5 mg. of promethazine (Phenergan - Wyeth); 7.5 mg. of triflupromazine (Vesprin - Squibb); and 2.5 mg. of perphenazine (Trilafon - Schering). Fifty mg. of cyclizine (Marezine - Burroughs Wellcome) was less effective, and 100 mg. of trimethobenzamide (Tigan - Roche) was not clearly effective at all. For the treatment of severe or persistent vomiting, J. Adriani, et al. (JAMA, 175: 666, 1961) found intravenous administration of promethazine (12.5 mg.), triflupromazine (2 mg.), fluphenazine (0.5 mg.), and trimethobenzamide (50 mg.) effective.

Phenothiazines other than those listed above may also be effective. Some surgeons prefer a parenteral antihistamine. The differences in experience with trimethobenzamide (Tigan) suggest the need for additional studies in postoperative use of this drug, particularly in view of its reported advantage of a lower incidence of side effects.

Medical Letter consultants do not recommend any antiemetic for routine prophylactic use. While there is little basis in present evidence for a clear choice among the various agents, they believe that Pentobarbital Sodium Injection, USP should be tried first when an antiemetic is needed, with an antihistamine or one of the drugs listed above as alternative choices.

PRO-DUOSTERONE AND EARLY DIAGNOSIS OF PREGNANCY

Pro-Duosterone (Roussel), a combination of ethisterone (50 mg.) and ethinyl estradiol (0.03 mg.) is promoted as the "3-day, oral test for early diagnosis of pregnancy." When amenorrhea which may be due to pregnancy occurs, one tablet is taken four times daily for three days; the manufacturer claims that "withdrawal" bleeding will follow within a few days after the last dose in a woman who is not pregnant and who previously had regular menstrual cycles; and that withdrawal bleeding will not occur in a pregnant woman.

SIGNIFICANCE OF TEST - With some qualification, these claims are correct. If withdrawal bleeding does occur, the amenorrhea was unquestionably not due to pregnancy; and there will be no withdrawal bleeding if the woman is pregnant. (Intramuscular injection of progesterones has been successfully used in the past to confirm pregnancy in this fashion, and other orally active progestins can also be employed for this purpose.)

While withdrawal bleeding rules out the possibility of pregnancy, however, the absence of withdrawal bleeding does not positively establish that the woman is pregnant. A false positive test — that is, the failure to induce menses — may occur in patients who have deep-seated emotional disorders such as anorexia nervosa or who have hypothalamic amenorrhea or prolonged functional amenorrhea.

The manufacturer's reference to a "3-day" test is misleading. In the major study cited to support the claims for Pro-Duosterone (G. E. Hayden, Amer. J. Obst. & Gyn., 76:271, 1958), pregnancy was confirmed in 64 patients by the use of progestins; in 27 of them ethisterone was the progestin used. Of 17 patients who were not pregnant, bleeding began between the third and the seventh day after withdrawal of medication in 15 cases, and even later in the remaining two. In general, withdrawal bleeding or menstruation may occasionally begin a day after the three days of therapy, but it may take as much as 14 days to start. Thus, if ovulation intervenes on the second or third day of medication, the menstrual period will not occur until approximately 12 to 14 days later.

LABORATORY TESTS - Laboratory tests for pregnancy require much less time; the Galli-Mainini frog test requires two hours; the rat ovary hyperemia test, 6 to 24 hours; the Friedman test, 30 to 48 hours. The progestin test may,

however, be utilized earlier in pregnancy than the animal tests, which is occasionally an advantage.

The manufacturer also claims that Pro-Duosterone actually protects pregnancy in habitual abortion, but there is no convincing evidence that this or any other progesterone, with or without an estrogen component, is effective in habitual abortion unless there is a defect in placental progesterone secretion. With such a defect, a few days of therapy cannot be expected to have any value.

In summary, where competent laboratory services are not readily available, Pro-Duosterone is safe and it is reasonably dependable in a woman who has been having regular menses. Urine specimens mailed to a distant laboratory are not dependable, since they may deteriorate or become "toxic" to the test animal. There is no reason to doubt that other progestins, including Norlutate (Parke, Davis) in doses of 5 mg. daily for three days, will work as well as Pro-Duosterone. A laboratory pregnancy test costs about $5 to $10; 12 tablets of Pro-Duosterone, about $4; three 5-mg. tablets of Norlutate, about $1.75.

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